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XXIII

Lung Cancer

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"It is essential to progress that we intensify our attack on this disease and study all possible methods that may contribute to its control. From the patient's point of view, in most instances, it is desirable to maintain an aggressive therapeutic approach." David A. Karnofsky[128]

Bronchogenic carcinoma is the most commonly lethal cancer in an increasing number of countries. The median survival from diagnosis remains below six months. The five-year survival barely approaches 10%.

The medical profession, allied sciences, and governments have acknowledged the challenge, as reflected in an increasing body of information in monographs from 25 countries. Effective prevention, early diagnosis, and improved therapy are within reach.

Cancers of the trachea, the pleura, and the lung, other than bronchogenic carcinoma, are included in the text, in consonance with List No. 162 of the World Health Organization for classification by site of origin.[270]

Historical Notes

The history of lung cancer starts with etiology and dates back to 1420, when the first mines were opened in Schneeberg, Saxony. Miners were known to develop "Bergsucht," called *morbus metallicorum imprimis pulmonum* by Theophrastus Bombastus Paracelsus of Hohenheim; it was described in the miners of Schneeberg by Agricola and others since the early sixteenth century.[195] After approximately a score of years, the miners became short of breath and had to change their occupations. Pneumoconiosis, chronic bronchitis, and tuberculosis were thought to be the underlying causes until 1879 when Härting and Hesse recognized among the miners an endemic of pulmonary "sarcoma," later classified as bronchogenic carcinoma.[106] This was attributed to cobalt, nickel, arsenic, the ubiquitous aspergillus, and finally to radon, for Eve Curie had obtained most of her uranium from Schneeberg. Subsequently, a high incidence of lung cancer was noted among uranium miners elsewhere.

Inhalation of cigarette smoke as the most common etiologic factor of lung cancer was first considered by Adler in 1912,[4] after Brosch's observation of epithelial proliferations in guinea pigs exposed to "tobacco juices" in 1900.[272] Roffo induced skin cancer in rabbits painted with tobacco tar containing 3,4-benzpyrene in 1930.[191] His observations were confirmed by others. Epidemiologic correlations were demonstrated by Hill and Doll, 1950,[115] then by Wynder and Graham, 1951,[271] and were widely confirmed. The public was fully informed. Unfortunately, this has not yet resulted in a reduction of cigarette consumption, and research toward development of a "safe" cigarette will have to be vigorously continued.

Van Swieten described the clinical and morphologic picture of lung cancer in *Com-*

Exhibit H

Clinical Manifestations. The wide spectrum of symptoms in patients with lung cancer provides important clues for the biologic behavior and anatomic extent of the tumor. Symptoms are related either to (1) the primary tumor, (2) invasion of adjacent structures, (3) extrathoracic metastases, or (4) systemic manifestations. Most types of symptoms occur in all major types of lung cancer. The frequency of given symptoms can be greatly influenced, however, by the specific types of lung cancer. The following generalizations apply for the majority of patients: (1) epidermoid carcinoma has the slowest growth rate and the lowest incidence of distant, hematogenous metastases; (2) small cell carcinoma shows the reverse behavior, with rapid growth and very early metastatic dissemination by both the hematogenous and lymphatic routes; (3) metastases in small cell carcinoma are present in more than 90% of the patients at the time of diagnosis; (4) adenocarcinoma and anaplastic large cell carcinoma take an intermediate position.

About 5% of all patients are asymptomatic at the time of diagnosis, and the suspicion of a pulmonary neoplasm is usually raised by abnormalities found fortuitously during routine x-ray examination of the chest. A higher proportion of adenocarcinoma is found in this group because of the tendency of this subtype to be located peripherally in the lung.

The duration of presenting symptoms is quite variable, dependent in part on cell type, and may be only six to eight weeks in duration for small cell and as long as four to six months for epidermoid carcinoma. Similarly, in the latter group the local pulmonary symptoms and signs are predominant, whereas in the former group extrathoracic manifestations occur more frequently.

Cough is the most common symptom related to either primary tumor or lymph node involvement. A change in the coughing pattern is seen when local complications occur. Bronchial obstruction commonly leads to atelectasis and infection behind the obstruction with persistent sputum production and abscess formation. This is more commonly seen with more centrally located epidermoid carcinomas and often complicates radiotherapy, when central tumor necrosis occurs. Similarly, hemoptysis, indicative of ulceration of the bronchial mucosa or of invasion into small bronchial vessels, is more suggestive of epidermoid carcinoma than of other cell types. Excessive pinkish, viscid sputum is typically seen in patients with bronchiolo-alveolar cell carcinoma. Stridor points to partial obstruction of a major part of the bronchial tree, but is much less common than changing rhonchi, owing to ineffectual tracheobronchial toilet. The tumor itself, or with its regional lymph node involvement, may cause a total bronchial occlusion with the formation of an obstructive pneumonia. Dyspnea may then be a prominent sign, but this can also be observed secondary to pleural effusion, extensive bilateral tumor invasion, or superior vena caval obstruction.

Obstruction of the superior vena cava occurs as a presenting symptom in approximately 4% of all patients, most frequently in epidermoid carcinoma and small cell carcinoma. The syndrome is due to obstruction of the blood flow through the superior cava either by extrinsic compression by the tumor or regional lymph nodes or by direct invasion with secondary thrombosis. Swelling of the neck, face, and upper extremities, especially after a night in recumbent position, associated with dilated veins in the upper half of the body and downward venous flow, is a typical feature of this syndrome.

Sharp localized unilateral chest pain is often caused by extension of the tumor into the chest wall. If the lesion is located in the upper part of the lung with invasion of the branchial plexus, the Pancoast or superior sulcus syndrome develops. Epidermoid carcinoma is the most frequent cell type to cause this syndrome, followed by adenocarcinoma. The syndrome includes the complaints of severe pain in the upper thorax with neuritic radiation to the homolateral upper extremity, almost always in the distribution of the lower roots of the brachial plexus first, sometimes limited exclusively to

the ulnar distribution. In addition, the cardinal findings of Horner's syndrome, including ptosis, miosis, enophthalmos, and decreased sweating of the face on the affected side, indicate stellate ganglion involvement, a common concomitant of superior sulcus tumors. Radiographically visible destruction of vertebral bodies and posterior parts of the upper ribs is common. It should be noted, however, that Pancoast syndrome is not pathognomonic for lung cancer. Recognition of the syndrome bears important prognostic and therapeutic implications.

Eight to ten per cent of all patients with bronchogenic carcinoma are hoarse at their initial consultation. This is a manifestation of laryngeal nerve involvement causing vocal cord paralysis. Less than 5% have dysphagia as a result of extrinsic esophageal compression.

Rarely, the initial symptomatology is caused by cardiac involvement; however, pericardial effusion or cardiac arrhythmia, secondary to myocardial invasion, may occur.

Extrathoracic Metastatic Symptoms. A high proportion of patients (20 to 35%, depending on patient selection) present with symptoms related to extrathoracic metastatic spread. Common nonspecific complaints include weight loss and fatigue, whereas more organ-specific symptoms may be related to metastases to supraclavicular lymph nodes, brain, abdominal organs, or bone. These symptoms occur more frequently in the small and large cell anaplastic tumors than in other cell types.

Convulsions, headache, nausea, personality changes, diplopia, and hemiplegia are the more common manifestations of cerebral metastases. All patients suspected of having brain tumors are also suspected of having lung cancer, since metastatic brain tumor is about as common as primary glioma (see XX-1).

Presenting abdominal manifestations are usually related to hepatic, pancreatic, or retroperitoneal lymph node involvement, and are typically seen in small cell carcinoma.

Bone metastases are also common, particularly in small cell carcinoma,[100] but are usually silent. However, dull bone pain, sometimes intermittent, may indicate local bone destruction. Pathologic fracture is rarely the presenting symptom. The lower thoracic and lumbar spine and pelvis are the most common sites of bone metastases, and destruction of a vertebral body may result in spinal cord compression with subsequent paralysis. Metastases to the adrenal, kidney, thyroid, gastrointestinal tract, and skin are frequently observed at autopsy, but rarely cause initial clinical symptomatology.

Extrathoracic Systemic Manifestations (Table XXIII-8). **Hypercalcemia.** The incidence of hypercalcemia ranges from 5 to 10% and is almost exclusively observed in patients with epidermoid carcinoma.[11,35] The classic symptoms include anorexia, nausea, drowsiness, constipation, polyuria, and polydipsia. Intensive search for bone lesions by roentgenograms, bone biopsies, or bone scans, or even by postmortem examinations results in negative findings in the majority of patients with hypercalcemia. This indicates that elevated serum calcium is commonly due to mechanisms other than osseous metastases: ectopic production of a parathormone-like substance by the tumor (see XVI-6 and XVI-9).

Ectopic ACTH Syndrome. The association between Cushing's syndrome and lung cancer was first described in 1928. Since that time, over 200 cases have been reported, largely in patients with small cell carcinoma and less frequently in the other major cell types and in bronchogenic carcinoid tumors. The clinical and metabolic manifestations are highly variable, and the typical Cushingoid features, such as cutaneous striae, pigmentation, obesity, and osteoporosis, occur in less than 50% of the patients. Symptoms related to hypokalemia, impaired glucose tolerance, and hypertension may be dominant. The urinary excretion of 17-hydroxycorticoids and 17 ketosteroids is increased, and in contrast to Cushing's disease, this excretion is not suppressed by corticosteroids, reflecting the autonomy of the tumor to produce ACTH. Successful treatment of the tumor is followed by disap-

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References
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TABLE XXIII-11. Incidence of hepatic metastases in lung cancer by cell type

Cell type	*Number of patients*	*% with hepatic metastases*	*References*
Epidermoid	1098*	30	29, 69, 132, 146, 212, 249, 252
	68†	11	273
Small	381*	60	132, 146, 249
	—	—	
Adenocarcinoma	483*	45	29, 69, 132, 146, 212, 249, 252
	12†	8.3	273
Large	179*	38	146
	46†‡	25	273

*Based on autopsy data
†Exclusively based on exploratory transdiaphragmatic laparotomy in a group of patients considered technically operable
‡Includes small cell carcinoma

of patients evaluated by transdiaphragmatic exploration or by exploratory laparotomy at the time of operation.[18,273] The use of liver scans with verification by liver biopsy, either percutaneously or during peritoneoscopy, might be of additional value in the detection of hepatic metastases.[101]

Similarly, scanning procedures with either ^{85}Sr or ^{18}F have been of increasing value in the detection of bone metastases, especially when complemented by a bone marrow examination of the posterior iliac crest.[101,104] These procedures are particularly valuable in the staging of patients with lung cancer of the small cell type.[104] Table XXIII-12 shows the incidence of osseous metastases at autopsy and in a series of consecutive untreated, inoperable patients with bronchogenic carcinoma. The commonly used radiographic bone survey is of limited value. Radiographically detected osseous lesions are usually osteolytic, especially in epidermoid cell and large cell carcinomas, whereas osteoblastic metastases sometimes develop in small cell carcinoma and adenocarcinoma.[103]

The occurrence of brain metastases at autopsy, compared to the incidence detected clinically, is summarized in Table XXIII-13. Again, the higher frequency of metastases from small cell carcinoma is noted. Cerebrospinal fluid examination, cytologic study, brain scans, electroencephalography, and arteriography are the main procedures used in the clinical search for brain metastases.

Of course, small metastatic lesions escape recognition with currently available

TABLE XXIII-12. Correlation between histologic cell type of lung cancer and osseous metastases including bone marrow

Cell type	*Number of patients*	*% with metastases*	*References*
Epidermoid	822*	24.0	29, 132, 146, 249, 251
	55†	3.6	101
Small	381*	35.4	132, 146, 249
	28†	45.0	101
Adenocarcinoma	288†	39.9	29, 132, 146, 249, 251
	27†	18.5	101
Large	179*	30.0	146
	40†	15.0	101

*Based on autopsy results
†Based on bone marrow examination exclusively in 150 consecutive, untreated, unresectable patients

TABLE XXIII-13. Incidence of brain metastases in lung cancer by cell type

Cell type	*Number of patients*	*% with brain metastases*	*References*
Epidermoid	352*	22	29, 99, 132, 146, 212
	51†	20	101
Small	143*	40	99, 132, 146,
	23†	39	101
Adenocarcinoma	139*	34	29, 99, 132, 146, 212
	25†	18	101
Large	123*	24	146
	35†	28	101

*Based on autopsy results
†Based on clinical data in 134 consecutive patients with bronchogenic carcinoma

methods, particularly in common extrathoracic sites such as retroperitoneal lymph nodes, adrenals, and pancreas.

Course

Four major factors determine the natural course of the disease: (1) the anatomic stage at the time of diagnosis, (2) the cell type, (3) the growth rate, and (4) prediagnositc symptomatology.

An evaluation of the influence of the pretherapeutic anatomic stage on survival has been hampered by the lack of both a uniform staging classification and the necessary diagnostic work-up as a basis for the staging. The staging system newly proposed by the American Joint Committee on Cancer Staging should be of definite value in this regard,[163] especially for comparing therapeutic results. The system is a refinement of the older widely accepted T (tumor) N (node) M (metastasis) system, previously used by several investigators,[204] and is described in Table XXIII-14. The staging is based on appropriate examinations, including physical examination, routine and special roentgenograms, bronchoscopy, esophagoscopy, mediastinoscopy, thoracentesis, thoracoscopy, and other special procedures designed to detect extrathoracic metastasis. Information obtained by thoracotomy might be used to establish a supplementary postoperative staging of the carcinoma with the TNM definitions. Each patient is assigned to the worst TNM category that most accurately describes the extent of his disease. Table XXIII-15 shows the correlation between the TNM classification and survival, excluding patients with small cell carcinoma. The survival of these latter patients corresponds to M-1 regardless of the recognizable anatomic extent of their disease. Therefore, it was concluded that any patient with this cell type should be regarded as having metastatic disease. Similar correlations between anatomic extent of disease and prognosis have been documented by a number of investigators using other staging systems.[204]

The extent of disease, as defined in the TNM classification, is categorized in four stages (Table XXIII-16). Stage 0, occult carcinoma, should become very uncommon with proper use of fiberoptic bronchoscopy. Stage 1 includes operable patients; stage 2, marginally operable patients; stage 3, inoperable patients. The latter should be further subdivided into regional disease, which can be included in an x-ray portal (T-3.1, T-3.2, T-3.3, N-1, N-2.1, N-2.2, M-0, M-1.1) and more extensive disease (M-1.2, M-1.3, and possibly M-1.1 to the contralateral side) beyond any hope for eradication or pronounced palliation by radiotherapy.

Further information regarding the natural course of disease of unresectable lung cancer is available from the Veterans Administration Lung Group,[121] which separates patients into "limited disease" (limited to one hemithorax with or without involvement of ipsilateral scalene nodes) as opposed to patients with more "extensive disease."

TABLE XXIII-14. The TNM system as basis for staging of lung cancer (American Joint Committee on Cancer Staging, 1972)

T = Primary Tumor
- T-0 Tumor proved by the presence of malignant cells in secretions but not visualized roentgenographically or bronchoscopically.
- T-1 A solitary tumor that is 3.0 cm. or less in greatest diameter, surrounded by lung or visceral pleura, and without evidence of invasion proximal to a lobar bronchus at bronchoscopy.
- T-2 A tumor more than 3.0 cm. in greatest diameter or a tumor of any size which, with its associated atelectasis or obstructive pneumonitis, extends to the hilar region. At bronchoscopy the proximal extent of demonstrable tumor must be at least 2.0 cm. distal to the carina. Any associated atelectasis or obstructive pneumonitis must involve less than an entire lung, and there must be no pleural effusion.
- T-3.1 A superior sulcus tumor having direct extrapulmonary extension.
- T-3.2 A tumor of any size associated with (a) atelectasis or obstructive pneumonitis of an entire lung and/or (b) a pleural transudate negative for malignant cells and/or (c) invasion of the chest wall.
- T-3.3 A tumor of any size (a) associated with a pleural exudate positive or negative for malignant cells, or (b) invading the mediastinum, or (c) less than 2.0 cm. distal to the carina.

N = Regional Lymph Nodes
- N-0 No demonstrable spread to the lymph nodes.
- N-1 Spread to lymph nodes in the ipsilateral hilar region.
- N-2.1 Spread to subcarinal lymph nodes and/or the ipsilateral mediastinal lymph nodes adjacent to the distal half of the intrathoracic trachea.
- N-2.2 Spread to any other mediastinal lymph node.

M = Distant Metastases
- M-0 No distant metastasis.
- M-1.1 Spread to scalene and/or supraclavicular lymph nodes.
- M-1.2 Spread to any other lymph nodes in the cervical area.
- M-1.3 Distant metastasis to liver, bone, brain, etc.

From Mountain.[163]

The difference between the two groups is illustrated in Figure XXIII-7.

Patients with "limited" disease lived substantially longer than those with "extensive" disease, with a median survival of 4.4 versus 2.9 months, respectively.

TABLE XXIII-15. Correlation between TNM factors and survival in lung cancer excluding small cell carcinoma in accordance with TNM classification of the American Joint Committee for Staging[163]

Stage	*Number of Cases*	*% Surviving*		
		1 year	*3 years*	*5 years*
T-1	206	73	50	43
T-2	719	50	27	21
T-3	753	27	9	7
N-0	855	56	33	27
N-1	258	41	17	12
N-2	455	21	5	3.5
M-0	1199	50	31	26
M-1	540	15	2.5	1

Of considerable interest are the VA Lung Group's data from the same category of "placebo-treated" patients with unresectable bronchogenic carcinoma, correlating the natural course to cell type (Fig. XXIII-8). The median survival for small cell carcinoma was 2.6 months versus 4.1, 4.4, and 4.3 months for epidermoid, adenocarcinoma, and large cell carcinoma, respectively.

Elmendorff,[68] in a similar group of inoperable patients, found the median survival for small cell carcinoma to be 3.6 months (128 patients), versus 4.5 months and 4.2 months for epidermoid (235 patients) and adenocarcinoma (40 patients), respectively. No significant difference was observed in the latter study comparing different age groups.